Gail model and breast cancer

Sir—H Jernström and colleagues (Nov 27, p 1846)[1] compared women with *BRCA1* and *BRCA2* mutations who developed breast cancer before age 40 years with mutation carriers who did not develop breast cancer by that age. They noted that parous women were at higher risk, and the increase in risk increased with the number of births.

Jernström and colleagues wrote: "Current models for integrating reproductive and familial risk factors may be inappropriate. For example, according to the model of Gail and colleagues,[2] a nulliparous woman with two affected relatives would be at higher risk of developing breast cancer than a woman with two affected relatives who had a child before age 20". In fact, the model of Gail and colleagues[2] includes a negative interaction between age at first live birth and number of affected first-degree relatives. As a result, early first live birth is associated with increased risk in women with two or more affected relatives but decreased risk in women with one or no affected relatives. In women with two affected relatives odds ratios from table 1[2] for first live birth at ages less than 20 years, 20–24 years, and 25–29 years (or nulliparous) compared with age 30 years or more were 1·63, 1·39, and 1·18, respectively. These data are similar to those of Jernström and colleagues, who noted an odds ratio of 1·71 for parous compared with nulliparous women. Thus, a factor that is protective in most women is not protective in women with a *BRCA1* or *BRCA2* mutation or in women with at least two affected first-degree relatives.

Bondy and colleagues[3] also found this negative interaction and increased risk from early first live births in women with at least two affected relatives. Costantino and colleagues[4] reviewed relative risk data from three other studies and found consistent evidence for a negative interaction between age at first live birth and number of affected relatives. The interaction was strong enough to render early age at first live birth a risk factor for breast cancer in women with two or more affected first-degree relatives in data from the Breast Cancer Prevention Trial, but not in data from the Cancer and Steroid Hormone Study, nor in data from the Nurses Health Study.

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1 Jernström H, Lerman C, Ghadirian P, et al. Pregnancy and risk of early breast cancer in carriers of *BRCA1* and *BRCA2*. *Lancet* 1999; **354:** 1846–50.
2 Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 1989; **81:** 1879–86.
3 Bondy ML, Lustbader ED, Halabi S, et al. Validation of a breast cancer risk assessment model in women with a positive family history. *J Natl Cancer Inst* 1994; **86:** 620–25.
4 Costantino JP, Gail MH, Pee D, et al. Validation studies for models projecting the risk of invasive and total breast cancer incidence. *J Natl Cancer Inst* 1999; **91:** 1541–48.

Prenatal diagnosis of acute lymphoblastic leukaemia

Sir—J L Wiemels and colleagues (Oct 30, p 1499)[1] have shown that it is likely that childhood acute lymphoblastic leukaemia (ALL) starts in utero in most cases. Together with the known concordance rate of childhood ALL in monozygotic twins,[2] which is probably around 5%, the investigators also conclude that the in-utero acquisition of t(12;21)(p13;q22) is in most cases insufficient to trigger an irreversible process of ALL leukaemogenesis. This conclusion, based on the known complexity of the somatic disease underlying carcinogenesis, is credible. However, this conclusion might be erroneous since it implicitly assumes that both twins harbour the *TEL-AML1* translocation at birth when this translocation occurs in one of them during prenatal life.

Do the investigators have evidence to support the idea that an in-utero graft of the non-malignant *TEL-AML1* clone occurs in virtually 100% of cases in monozygotic twins? If such evidence is lacking, one could also hypothesise that the 5% concordance rate could be explained by a 5% probability of successful in-utero graft together with a 100% probability of malignant transformation of the *TEL-AML1* clone.

Definitive proof of the investigators' conclusion could be given by a study showing that each healthy twin in non-concordant twin cases for *TEL-AML1* childhood ALL is an asymptomatic carrier of a non-malignant clone with the *TEL-AML1* translocation.

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2 Buckley JD, Buckley CM, Breslow NE, et al. Concordance for childhood cancer in twins. *Med Pediatr Oncol* 1996; **26:** 223–29.

Authors' reply

Sir—Nicolas Janin suggests that our interpretation of the modest (−5%) concordance rate of acute lymphoblastic leukaemia (ALL) in identical twins might be incorrect. An alternative view is that the fetal clone initiated in one twin by TEL-AML1 gene fusion might engraft the co-twin in only 5% of such twin pairs but have a 100% probability of transformation to overt malignancy. This is indeed a formal possibility but is, we believe, unlikely. First, *TEL-AML1* fusion by itself appears to be insufficient for leukaemogenesis as judged by the lack of leukaemia in mice transgenic for *TEL-AML1* (A M Ford and M F Greaves, unpublished observations; B Young and O Bernard, personal communication). Second, epidemiological evidence, albeit incomplete, suggests that postnatal exposures, probably of an infectious nature, are involved and necessary for the development of ALL.[1,2]

We agree with Janin that formal proof of our preferred interpretation would be helpful and could come from the observation of *TEL-AML1* positive cells in the blood or marrow of a healthy monozygotic co-twin of a patient with ALL. We are already attempting to do this experiment, which poses several ethical and logistic difficulties. Our model of the natural history of childhood common ALL[3] predicts that we will find low level but PCR-detectable *TEL-AML1* clone-specific sequences in the circulation of healthy co-twins, but only in most of the 60% or so that have monochorionic placentas.[4] Another important prediction of our model is that considerably more children should be born with a *TEL-AML1* fusion gene in lymphoid cells than ever develop ALL with the *TEL-AML1* gene fusion (about one in 12 500). This we are attempting to confirm by reverse transcriptase PCR screening of unselected normal newborn cord blood.

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2 Little J. Epidemiology of childhood cancer. Lyon: IARC Scientific Publications, 1999.
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4 Strong SJ, Corney G. The placenta in twin pregnancy. Oxford: Pergamon, 1967.